PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 12551050/EJH/ar	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. **PCT**/AU2004/001840	International filing date *(day/month/year)* 23 December 2004	Priority date *(day/month/year)* 24 December 2003

International Patent Classification (IPC) or national classification and IPC

Int. Cl.

A61K 38/45 (2006.01) ***A61P 35/00*** (2006.01)
A61K 38/19 (2006.01) ***A61P 37/02*** (2006.01)

Applicant

THE WALTER AND ELIZA HALL INSTITUTE OF MEDICAL RESEARCH et al

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. [X] *(sent to the applicant and to the International Bureau)* a total of **5** sheets, as follows:
      - [ ] sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      - [ ] sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. [ ] *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or table related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:

[X]	Box No. I	Basis of the report
[ ]	Box No. II	Priority
[ ]	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
[ ]	Box No. IV	Lack of unity of invention
[X]	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
[ ]	Box No. VI	Certain documents cited
[ ]	Box No. VII	Certain defects in the international application
[X]	Box No. VIII	Certain observations on the international application

Date of submission of the demand 24 October 2005	Date of completion of this report 28 April 2006
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **JENNIFER FERNANCE** Telephone No. (02) 6283 2269

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/AU2004/001840

Box No. I Basis of the report

1. With regard to the **language,** this report is based on:

[X] The international application in the language in which it was filed

[ ] A translation of the international application into , which is the language of a translation furnished for the purposes of:

- [ ] international search (under Rules 12.3(a) and 23.1 (b))
- [ ] publication of the international application (under Rule 12.4(a))
- [ ] international preliminary examination (Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

[ ] the international application as originally filed/furnished

[X] the description:

pages **1-51** as originally filed/furnished
pages* received by this Authority on with the letter of
pages* received by this Authority on with the letter of

[X] the claims:

pages as originally filed/furnished
pages* as amended (together with any statement) under Article 19
pages* **52-56** received by this Authority on **1 March 2006** with the letter of **1 March 2006**
pages* received by this Authority on with the letter of

[X] the drawings:

pages **1/5-5/5** as originally filed/furnished
pages* received by this Authority on with the letter of
pages* received by this Authority on with the letter of

[ ] a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. [ ] The amendments have resulted in the cancellation of:

- [ ] the description, pages
- [ ] the claims, Nos.
- [ ] the drawings, sheets/figs
- [ ] the sequence listing *(specify)*:
- [ ] any table(s) related to the sequence listing *(specify)*:

4. [ ] This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- [ ] the description, pages
- [ ] the claims, Nos.
- [ ] the drawings, sheets/figs
- [ ] the sequence listing *(specify)*:
- [ ] any table(s) related to the sequence listing *(specify)*:

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims 11, 12, 26, 27	**YES**
	Claims 1-10, 13-25	**NO**
Inventive step (IS)	Claims -	**YES**
	Claims 1-27	**NO**
Industrial applicability (IA)	Claims 1-27	**YES**
	Claims -	**NO**

2. Citations and explanations (Rule 70.7)

The following documents identified in the International Search Report have been considered for the purposes of this report:

D1 MALISZEWSKI C
D2 MOREL P et al
D3 US 2003/0113341
D4 MCNEEL D et al
D5 DONG J et al
D6 RINI B I et al

New Citation:

D7: WO 1994/028391 A (Immunex Corp) 8 December 1994

Novelty (N) Claims 1-10 and 13-25

D7 disclose the use of Flt-3 L in the treatment of HIV infections and impeding the development of AIDS from HIV infections, cancer and aplastic anaemia (Abstract, pages 4-6, 8-10, 36, 37, 40, 41 and claims).

Due to the lack of the provision of a definition of a "Flt-3-Flt-3L receptor agonist", this report has been established on the premise that the term refers to a selective Flt-3 agonist, not an Flt-3 antagonist. This lack of definition was raised in the Opinions under clarity and is presently maintained (see Box VIII).

D1 discloses the use of Flt-3 L in the treatments of cancer, infectious diseases, autoimmunity and other pathologies. D3-D6 disclose the use of Flt-3L in the treatments of cancer alone or in combination with other therapies including cytokines. Each citation attributes the activity to the expansion of dendritic cells. The same subjects are being treated with the same agents to achieve the same outcome. In the case of claims 1-12, the outcome is the prevention of an autoimmune disease. Autoimmune diseases include diabetes and the progression of HIV to AIDS as disclosed in D7.

The limitation that the Flt-3 L increases a specific sub-type of dendritic cells or induces and maintains immune tolerance is not considered a true limitation in that the administration of Flt-3L in autoimmune conditions would inherently have this activity. Claims 13-27 are only limited to the modulation of tolerogenicity or the modulation of the level of immune tolerance and therefore they encompass the induction of an immune response. The additional features of the claims, that is, the form of administration of the combination, the source of the Flt-3L or Flt-3-Flt-3L receptor agonist, the choice of antigen or the animal to be treated do not add novelty to the claims. The Skilled Addressee would appreciate that these features would not affect the working of the invention. Therefore claims 1-10 and 13-25 lack novelty in light of D1 and D3-D7.

Claims 11, 12, 26 and 27 meet the criteria set forth in PCT Article 33(2) for novelty. The prior art published before the priority date does not disclose the treatment of the conditions defined in these claims.

(Continued in Supplemental Box)

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The specification is not clear.

- The specification describes "Flt3-L" and "FL" as the same ligand.
- The description describes "plasmacytoid" and "plastacytoid" dendritic cells (for example, see pages 2, 4, 8, and claims).

It is not clear if the "Flt-3-Flt-3L receptor agonist" is a selective Flt-3 agonists or an Flt-3 antagonist. This objection should be addressed as the two terms have opposing activities.

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of Box V:

Inventive Step Claims 1-27

Claims 1-10 and 13-25 as for novelty.

The specification describes the treatment of an autoimmune disease as attacking the pathogenic agent that causes the disease. D1 and D3-D6 disclose the use of Flt-3L as an adjuvant. The antigen is disclosed as one that may be either already present in the subject or may be administered with the ligand. The choice of antigen as defined in claims 1, 11, 26 and 27 is not considered inventive.

D2 discloses the use of expanded dendritic cells in the treatment of diabetes in NOD mice. It also discloses that FLT-3L will expand the presently defined subtypes *in vivo*. It is considered the person Skilled in the Art would investigate the use of Flt-3L or Flt-3-Flt-3L receptor agonist in the treatment of diabetes. Therefore claims 11, 12, 26 and 27 lack inventive step in light of D2.

D1 or D2-D6 either alone or in combination with D2 would also deprive claims 12, 26 and 27 inventive step.

Industrial Applicability (IA) Claims 1-27

The invention defined in the claims is considered to meet the requirements of Industrial Applicability under Article 33(4) of the PCT because it can be made by, or used in, industry.

CLAIMS:

1. A method for preventing onset of an autoimmune disease in a subject said method comprising administering to said subject Flt-3L or a Flt-3-Flt-3L receptor agonist in an amount effective to increase a sub-type of non-activated, immature and tolerogenic DC selected from Plasmacytoid DC and $CD8^+$ DC or their equivalents thereby inducing or maintaining immune tolerance in said subject.

2. The method of Claim 1 wherein the agent is Flt-3L.

3. The method of Claim 1 or 2 wherein the Flt-3L or a Flt-3-Flt-3L receptor agonist is co-administered with a cytokine.

4. The method of Claim 2 or 3 wherein the Flt-3L or a Flt-3-Flt-3L receptor agonist is co-administered with a Toll-like receptor ligand.

5. The method of Claim 3 or 4 wherein co-administration is sequential administration.

6. The method of Claim 3 or 4 wherein co-administration is simultaneous administration.

7. The method of Claim 1 wherein the subject is a human, non-human primate, livestock animal, laboratory test animal, a companion animal, a captured wild animal or an avian species.

8. The method of Claim 7 wherein the subject is a human.

9. The method of Claim 1 wherein the Flt-3L is derived from the same species to which it is administered.

10. The method of Claim 1 wherein the Flt-3L is derived from a different species to which it is administered.

11. The method of Claim 1 wherein the autoimmune disease is Active Chronic Hepatitis, Addison's Disease, Anti-phospholipid Syndrome, Atopic Allergy, Autoimmune Atrophic Gastritis, Achlorhydra Autoimmune, Celiac Disease, Crohns Disease, Cushings Syndrome, Dermatomyositis, Type I Diabetes, Discoid Lupus, Erythematosis, Goodpasture's Syndrome, Grave's Disease, Hashimoto's Thyroiditis, Idiopathic Adrenal Atrophy, Idiopathic Thrombocytopenia, Insulin-dependent Diabetes, Lambert-Eaton Syndrome, Lupoid Hepatitis, Lymphopenia, Mixed Connective Tissue Disease, Multiple Sclerosis, Pemphigoid, Pemphigus Vulgaris, Pernicious Anema, Phacogenic Uveitis, Polyarteritis Nodosa, Polyglandular Auto. Syndromes, Primary Biliary Cirrhosis, Primary Sclerosing Cholangitis, Psoriasis, Raynauds, Reiter's Syndrome, Relapsing Polychondritis, Rheumatoid Arthritis, Schmidt's Syndrome, Scleroderma – CREST, Sjogren's Syndrome, Sympathetic Ophthalmia, Systemic Lupus Erythematosis, Takayasu's Arteritis, Temporal Arteritis, Thyrotoxicosis, Type B Insulin Resistance, Ulcerative Colitis and Wegener's Granulomatosis.

12. The method of Claim 11 wherein the autoimmune disease is diabetes.

13. A method of modulating the degree of tolerogenicity in a subject, or modulating the level of immune tolerance against cancer or a pathogenic agent said method comprising administering to said subject Flt-3L or Flt-3-Flt-3L receptor agonist in an amount effective to preferably increase a sub-type of non-activated, immature and tolerogenic DC selected from Plasmacytoid DC and $CD8^+$ DC or their equivalents in said subject.

14. The method of Claim 13 wherein the agent is Flt-3L.

15. The method of Claim 13 or 14 wherein the Flt-3L or a Flt-3-Flt-3L receptor agonist is co-administered with a Toll-like receptor ligand.

16. The method of Claim 14 or 15 wherein co-administration is sequential administration.

17. The method of Claim 14 or 15 wherein co-administration is simultaneous administration.

18. The method of Claim 13 wherein the subject is a human, non-human primate, livestock animal, laboratory test animal, a companion animal, a captured wild animal or an avian species.

19. The method of Claim 18 wherein the subject is a human.

20. The method of Claim 13 wherein the Flt-3L is derived from the same species to which it is administered.

21. The method of Claim 13 wherein the Flt-3L is derived from a different species to which it is administered.

22. The method of Claim 13 in the treatment of cancer.

23. The method of Claim 22 wherein the cancer is ABL1 protooncogene, AIDS Related Cancers, Acoustic Neuroma, Acute Lymphocytic Leukaemia, Acute Myeloid Leukaemia, Adenocystic carcinoma, Adrenocortical Cancer, Agnogenic myeloid metaplasia, Alopecia, Alveolar soft-part sarcoma, Anal cancer, Angiosarcoma, Aplastic Anaemia, Astrocytoma, Ataxia-telangiectasia, Basal Cell Carcinoma (Skin), Bladder Cancer, Bone Cancers, Bowel cancer, Brain Stem Glioma, Brain and CNS Tumors, Breast Cancer, CNS Tumors, Carcinoid Tumors, Cervical Cancer, Childhood Brain Tumors, Childhood Cancer, Childhood Leukaemia, Childhood Soft Tissue Sarcoma, Chondrosarcoma, Choriocarcinoma, Chronic Lymphocytic Leukaemia, Chronic Myeloid Leukaemia, Colorectal Cancers, Cutaneous T-Cell Lymphoma, Dermatofibrosarcoma-protuberans, Desmoplastic-Small-Round-Cell-Tumor, Ductal Carcinoma, Endocrine

Cancers, Endometrial Cancer, Ependymoma, Esophageal Cancer, Ewing's Sarcoma, Extra-Hepatic Bile Duct Cancer, Eye Cancer, Eye: Melanoma, Retinoblastoma, Fallopian Tube cancer, Fanconi Anaemia, Fibrosarcoma, Gall Bladder Cancer, Gastric Cancer, Gastrointestinal Cancers, Gastrointestinal-Carcinoid-Tumor, Genitourinary Cancers, Germ Cell Tumors, .Gestational-Trophoblastic-Disease, Glioma, Gynaecological Cancers, Haematological Malignancies, Hairy Cell Leukaemia, Head and Neck Cancer, Hepatocellular Cancer, Hereditary Breast Cancer, Histiocytosis, Hodgkin's Disease, Human Papillomavirus, Hydatidiform mole, Hypercalcemia, Hypopharynx Cancer, IntraOcular Melanoma, Islet cell cancer, Kaposi's sarcoma, Kidney Cancer, Langerhan's-Cell-Histiocytosis, Laryngeal Cancer, Leiomyosarcoma, Leukaemia, Li-Fraumeni Syndrome, Lip Cancer, Liposarcoma, Liver Cancer, Lung Cancer, Lymphedema, Lymphoma, Hodgkin's Lymphoma, Non-Hodgkin's Lymphoma, Male Breast Cancer, Malignant-Rhabdoid-Tumor-of-Kidney, Medulloblastoma, Melanoma, Merkel Cell Cancer, Mesothelioma, Metastatic Cancer, Mouth Cancer, Multiple Endocrine Neoplasia, Mycosis Fungoides, Myelodysplastic Syndromes, Myeloma, Myeloproliferative Disorders, Nasal Cancer, Nasopharyngeal Cancer, Nephroblastoma, Neuroblastoma, Neurofibromatosis, Nijmegen Breakage Syndrome, Non-Melanoma Skin Cancer, Non-Small-Cell-Lung-Cancer-(NSCLC), Ocular Cancers, Oesophageal Cancer, Oral cavity Cancer, Oropharynx Cancer, Osteosarcoma, Ostomy Ovarian Cancer, Pancreas Cancer, Paranasal Cancer, Parathyroid Cancer, Parotid Gland Cancer, Penile Cancer, Peripheral-Neuroectodermal-Tumors, Pituitary Cancer, Polycythemia vera, Prostate Cancer, Rare-cancers-and-associated-disorders, Renal Cell Carcinoma, Retinoblastoma, Rhabdomyosarcoma, Rothmund-Thomson Syndrome, Salivary Gland Cancer, Sarcoma, Schwannoma, Sezary syndrome, Skin Cancer, Small Cell Lung Cancer (SCLC), Small Intestine Cancer, Soft Tissue Sarcoma, Spinal Cord Tumors, Squamous-Cell-Carcinoma-(skin), Stomach Cancer, Synovial sarcoma, Testicular Cancer, Thymus Cancer, Thyroid Cancer, Transitional-Cell-Cancer-(bladder), Transitional-Cell-Cancer-(renal-pelvis-/-ureter), Trophoblastic Cancer, Urethral Cancer, Urinary System Cancer, Uroplakins, Uterine sarcoma, Uterus Cancer, Vaginal Cancer, Vulva Cancer, Waldenstrom's-Macroglobulinemia, Wilms' Tumor.

24. The method of Claim 22 in the prophylaxis of a pathogenic agent-induced autoimmune disease.

25. The method of Claim 24 wherein the autoimmune disease is Active Chronic Hepatitis, Addison's Disease, Anti-phospholipid Syndrome, Atopic Allergy, Autoimmune Atrophic Gastritis, Achlorhydra Autoimmune, Celiac Disease, Crohns Disease, Cushings Syndrome, Dermatomyositis, Type I Diabetes, Discoid Lupus, Erythematosis, Goodpasture's Syndrome, Grave's Disease, Hashimoto's Thyroiditis, Idiopathic Adrenal Atrophy, Idiopathic Thrombocytopenia, Insulin-dependent Diabetes, Lambert-Eaton Syndrome, Lupoid Hepatitis, Lymphopenia, Mixed Connective Tissue Disease, Multiple Sclerosis, Pemphigoid, Pemphigus Vulgaris, Pernicious Anema, Phacogenic Uveitis, Polyarteritis Nodosa, Polyglandular Auto. Syndromes, Primary Biliary Cirrhosis, Primary Sclerosing Cholangitis, Psoriasis, Raynauds, Reiter's Syndrome, Relapsing Polychondritis, Rheumatoid Arthritis, Schmidt's Syndrome, Scleroderma – CREST, Sjogren's Syndrome, Sympathetic Ophthalmia, Systemic Lupus Erythematosis, Takayasu's Arteritis, Temporal Arteritis, Thyrotoxicosis, Type B Insulin Resistance, Ulcerative Colitis and Wegener's Granulomatosis.

26. The method of Claim 25 wherein the autoimmune disease is diabetes.

27. The method of Claim 26 wherein the autoimmune disease is viral-induced diabetes.